Visit-to-Visit Fasting Glucose Variability in Young Adulthood and Hippocampal Integrity and Volume at Midlife

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Diabetes Care 2019;42:2334–2337 | https://doi.org/10.2337/dc19-0834

OBJECTIVE

To determine whether visit-to-visit fasting glucose (VVFG) variability in young adulthood is associated with midlife hippocampal integrity and volume.

RESEARCH DESIGN AND METHODS

Multivariable-adjusted linear regression models were used to estimate the association between VVFG variability and brain MRI variables in 543 CARDIA study participants. VVFG variability was defined by the SD of FG (SD_{FG}), the coefficient of variation of the mean FG (CV_{FG}), and the average real variability (ARV_{FG}) over 25 years of follow-up. Hippocampal integrity fractional anisotropy (FA) and tissue volume standardized to intracranial volume were measured by 3T MRI at year 25.

RESULTS

After multivariable adjustment, higher FG variability (1-SD increase) was associated with lower hippocampal FA (SD_{FG} −0.015 [95% CI −0.026, −0.004]; CV_{FG} −0.009 [95% CI −0.018, −0.001]; ARV_{FG} −0.011 [95% CI −0.019, −0.002]) and lower hippocampal volume (SD_{FG} −0.012 [95% CI −0.023, −0.001]).

CONCLUSIONS

Higher VVFG variability in young adulthood is associated with lower midlife hippocampal integrity and volume, suggesting its value in predicting risk for hippocampal structural damage.

NOVEL COMMUNICATIONS IN DIABETES

According to the American Diabetes Association, diabetes is associated with an increased risk and rate of cognitive decline (1). The increasing prevalence of prediabetes and diabetes necessitates a better understanding of the impact of these disorders on cerebral structure and function (2). Given the association between fasting glucose (FG) variability and cognitive function (3), we hypothesized that FG variability may be associated with hippocampal structure.

RESEARCH DESIGN AND METHODS

Study Population

The Coronary Artery Risk Development in Young Adults (CARDIA) study was a multicenter prospective study that recruited 5,115 healthy black and white young adults initially aged 18–30 years in 1985 and 1986 from four U.S. field centers. Follow-up examinations were conducted at years 2, 5, 7, 10, 15, 20, 25, and 30 after

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Received 26 April 2019 and accepted 30 August 2019

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-0834/-/DC1.

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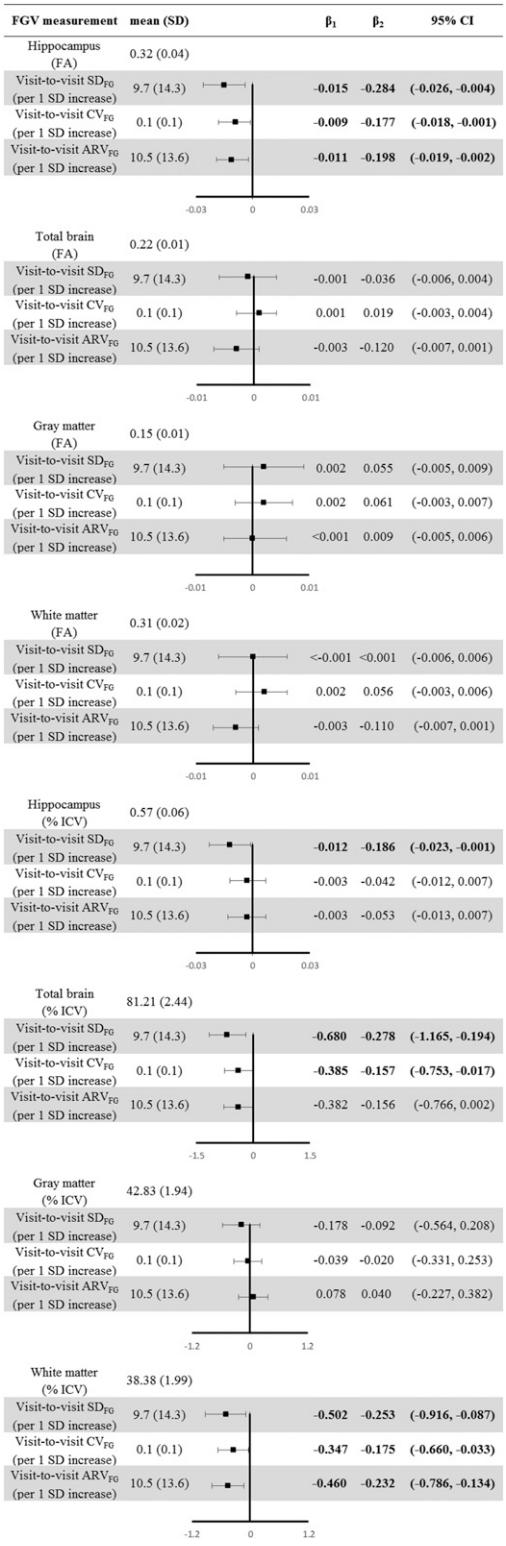

Figure 1—The forest plot of association between VVFG variability in young adulthood and brain integrity and volume at middle age over 25 years ($n = 543$). FA values of the hippocampus, total brain, gray matter, and white matter were log transformed before analyses. Each normal brain volume was standardized by dividing each by the intracranial volume (ICV). β_1 represents the unstandardized regression coefficient, and β_2 represents the standardized regression coefficient. Adjusted β (95% CI) associated with a 1-SD increment of each FG variability (FGV) parameter is shown. One-SD increment of each variable is as follows: $SD_{FG} = 14.3$ mg/dL, $ARV_{FG} = 13.6$ mg/dL, and $CV_{FG} = 0.1$. As adjustment factors, all models include demographic variables (age at year 25, sex, race, and education), clinical characteristics at year 25 (BMI, smoking, drinking, physical activity, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, and HbA_{1c}),

the baseline (year 0). The retention rate across examinations was 72% at year 25, and a subsample of the retained participants was invited to participate in a CARDIA brain MRI substudy. Participants in this substudy were recruited from three of the four CARDIA field centers. The exclusion criteria for the MRI substudy were any contraindication for MRI, suspected pregnancy, or a body that was too large for the MRI chamber. All participants provided written informed consent for each study, and the institutional review boards at each study site and at the coordinating center granted approval annually for all examinations.

Of the 719 participants who underwent MRI scans in the CARDIA study, we excluded participants without MRI data ($n = 22$), FG data ($n = 144$), and baseline covariates ($n = 10$).

Clinical Measurement

Standardized protocols for data collection were used across study centers and for each examination. All participants were asked to fast and to avoid smoking or heavy physical activity for at least 12 h before each examination. Demographic and clinical characteristics as well as medical history data were collected for statistical analysis.

FG

FG was assayed at baseline using the hexokinase ultraviolet method by American Bio-Science Laboratories and at subsequent examinations in years 7, 10, 15, 20, and 25 using hexokinase coupled to glucose-6-phosphate dehydrogenase. The data were recalibrated to normalize the glucose values across CARDIA examinations.

Brain MRI

Detailed information on the scanners, training of MRI technologists at the different sites, implementation of the study protocols, and quality assurance of scanner stability and performance is given in the Supplementary Data. In this study, we analyzed diffusion tensor imaging–derived fractional anisotropy (FA) values and determined the total bilateral hippocampal volume. The clinical relevance of hippocampal FA as a measurement of hippocampal integrity has been reported previously (4).

Statistical Analyses

Descriptive statistics, including the means and SDs, were obtained for continuous variables, and proportions were determined for categorical variables. We assessed the correlations between visit-to-visit FG (VVFG) variability and clinical characteristics by Pearson correlation analysis. Multivariable-adjusted linear regression models were used to estimate the associations between FG variability and brain MRI variables. The main parameters determined were the SD of FG (SD_{FG}), the coefficient of variation of the mean FG (CV_{FG}), and the average real variability (ARV_{FG}), and the main outcomes were hippocampal integrity and normal tissue volume (hippocampal FA and [hippocampus volume $\times$ 100]/intracranial volume, respectively). We also assessed the association of FG variability with total brain, gray matter, and white matter volume.

The FA measurements were log transformed before analysis. We adjusted for demographic variables, clinical characteristics, medication use, and weighted mean FG measurements. In addition, we performed two sensitivity analyses.

A two-sided *P* value <0.05 was considered to indicate statistical significance. All analyses were performed with SPSS version 18.0.

RESULTS

The baseline demographic and clinical characteristics and the associations between VVFG variability and clinical characteristics are presented in the Supplementary Data. After multivariable adjustment, higher FG variability (1-SD increment) (unstandardized regression coefficient [standardized regression coefficient] [95% CI]) was associated with lower hippocampal FA (SD_{FG} −0.015 [−0.284] [−0.026, −0.004]; CV_{FG} −0.009 [−0.177] [−0.018, −0.001]; ARV_{FG} −0.011 [−0.198] [−0.019, −0.002]) and lower hippocampal volume (SD_{FG} −0.012 [−0.186] [−0.023, −0.001]). Furthermore, higher FG variability (1-SD increment) was associated with lower total brain volume (SD_{FG} −0.680 [−0.278] [−1.165, −0.194]; CV_{FG} −0.385 [−0.157] [−0.753, −0.017]) and lower white matter volume (SD_{FG} −0.502 [−0.253] [−0.916, −0.087]; CV_{FG} −0.347 [−0.175] [−0.660, −0.033]; ARV_{FG} −0.460 [−0.232] [−0.786, −0.134]) (Fig. 1).

In the two sensitivity analyses, the results were similar when participants not taking antidiabetic medications were excluded ($n = 509$) (Supplementary Figs. 1 and 2) and when FG variability was calculated from year 7 to year 25 ($n = 548$) (Supplementary Figs. 3 and 4).

CONCLUSIONS

In this study, we observed that higher FG variability in young adulthood was independently associated with lower hippocampal integrity and volume at middle age. Additionally, we found that higher SD_{FG} in young adulthood was associated with lower white matter and total brain volume at middle age, that higher CV_{FG} was associated with lower white matter and total brain volume at middle age, and that higher ARV_{FG} was associated with lower white matter volume at middle age.

Previous studies have revealed that FG variability in young adulthood is associated with cognitive function in middle age (3). This finding indicates the potential significance of FG variability in identifying individuals with a high risk of cognitive dysfunction. Our study partly explains the mechanisms by which FG variability affects cognitive function through damage to brain tissue structure. Several potential mechanisms may contribute to the association between VVFG variability and the hippocampus. First, hyperglycemia influences nerve cell function and causes changes in brain tissue structure (5). In vitro, compared with constant high glucose levels, short-term fluctuations in glucose levels are associated with greater neuronal mitochondrial dysfunction and stress as well as with DNA damage and oxidative stress in endothelial cells (6). Second, high FG may alter blood flow and lead to vascular damage, increasing the risk of stroke (7,8). Among individuals with diabetes, acute FG variability is associated with endothelial dysfunction and vascular damage beyond that caused by elevated mean glucose concentrations (9,10). Finally, glucose metabolism is involved in the development of cerebral arterial stiffness, which leads to abnormal brain tissue structure (11–13).

To our knowledge, our study is the first comprehensive report on the association of VVFG variability in young adults with hippocampal integrity and volume. In the past, clinical practitioners have concentrated on patients' acute FG levels rather than on long-term FG variability. Our findings provide new insight into the relationship between FG variability and cognitive dysfunction. Further research on the mechanism should be conducted.

The strengths of this study include a prospective study design with 25 years of follow-up from young adulthood to middle age, standardized data collection protocols, and strict quality control. However, several limitations should be considered. First, the time between follow-up visits precluded frequent FG measurements in the participants. The relatively infrequent FG measurements may have influenced the identification of the association between FG variability and hippocampal structure. Second, the smaller changes contributing to the overall alterations in hippocampal integrity and volume were not ascertained. Thus, we could not consider whether these changes in brain structure were associated with FG variability. Third, the lack of cognitive measures in this study is a limitation, as we did not determine whether cognitive decline was associated with the hippocampal structural changes in our study. Finally, this study was observational, and our results may be unsuitable for direct use in clinical practice. FG variability has been reported to be associated with lifestyle factors (14). Consequently, this parameter may be useful for identifying young adults who may benefit from lifestyle modifications to maintain healthy brain function. The observed changes in hippocampal integrity and volume were very small but sufficient to affect cognitive function. Our study provides new insights regarding the risk factors for cognitive dysfunction.

medication use (antihypertensive, antidiabetic, and lipid lowering) from year 0 to 25, and weighted mean FG measurement. Statistical significance was defined as $P < 0.05$.

In summary, higher VVFG variability in young adulthood is associated with lower hippocampal integrity and volume at midlife. This finding may be valuable for evaluating the potential risk for hippocampal structural damage.

Acknowledgments. The authors thank the staff and participants of the CARDIA study for their significant contributions.

Funding. This work was supported by the National Natural Science Foundation of China (81600206 to X.Zhu. and 81870195 to X.L.) and the Natural Science Foundation of Guangdong Province (2016A030310140 to X.Zhu. and 20160903 to X.L.). The CARDIA study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN268201300025C and HHSN268201300026C), Northwestern University (HHSN268201300027C), University of Minnesota (HHSN268201300028C), Kaiser Foundation Research Institute (HHSN268201300029C), and Johns Hopkins University School of Medicine (HHSN268200900041C). CARDIA is also partially supported by the Intramural Research Program of the National Institute on Aging (NIA) and an intra-agency agreement between NIA and NHLBI (AG0005). This article has been reviewed by CARDIA for scientific content.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. Z.X., J.L., and S.Z. performed statistical analysis. Z.X., J.L., X.Zhu., and X.L. conceived the research idea and designed the study. Z.X., H.Z., and Y.C. drafted the manuscript. J.L., X.Zho., and X.S. analyzed and interpreted data. X.Zhu. and X.L. acquired data. Each author contributed important intellectual content during manuscript writing or revision. Z.X., J.L., X.Zho., S.Z., X.S., H.Z., Y.C., X.Zhu., and X.L. read and approved the final manuscript. X.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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